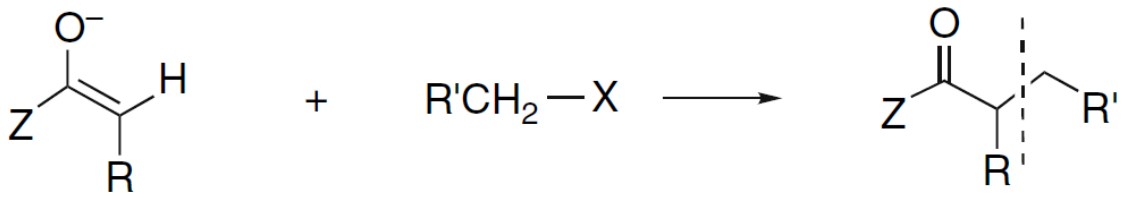
Alkylation with Enolates and Carbon Nucleophiles

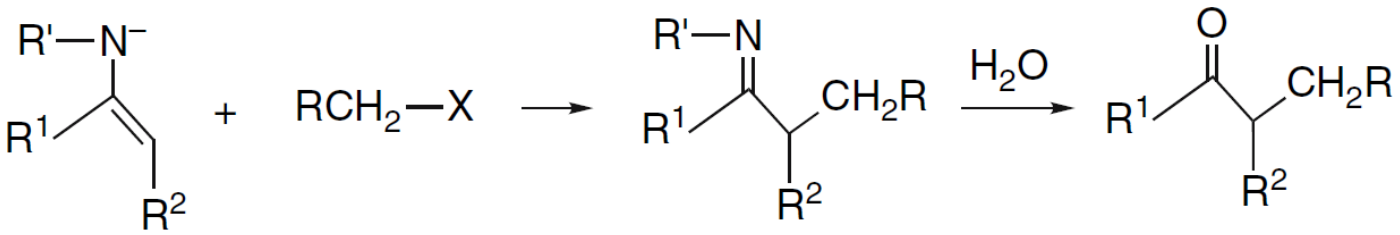
- chemistry of *enolates, imine anions, and enamines*
- carbon nucleophiles
- reaction with alkylating reagents (S_N2) – formation of C-C

enolate:



$Z = R, RO, R_2N$ enolate alkylation

imine anion:



- the crucial factors :
  - a) the conditions for generation of the carbon nucleophile
  - b) the effect of the reaction conditions on the structure and reactivity of the Nu
  - c) the regio- and stereoselectivity of the alkylation reaction (1°, 2°- alkyl)

- various carbonyl compounds: ketones, esters, amides, etc.

Alkylation with Enolates and Carbon Nucleophiles

Generation of Enolates by Deprotonation

- electron-withdrawing substituents cause very large increases in the acidity of C–H
- strong anion stabilizing effect on carbanions:

$$NO_2 > C{=}O > CO_2R \sim SO_2 \sim CN > CONR_2$$

- polar and resonance effect

- pK (DMSO) – larger, stabilization
- anions are strongly basic in DMSO then in water

- basicity function H_-
- larger the value of H_-, the greater the H-abstracting ability of the medium

$$RH + B^- \rightleftharpoons R^- + BH$$

$$pK_{RH} = H_- + \log \frac{[RH]}{[R^-]}$$

Compound	pK
CH_3NO_2	17.2
CH_3COPh	24.7
CH_3COCH_3	26.5
CH_3SO_2Ph	29.0
$CH_3CO_2C_2H_5$	30.5[b]
$CH_3SO_2CH_3$	31.1
CH_3CN	31.3
$CH_3CON(C_2H_5)_2$	34.5[b]

Representative Solvent-Base Systems

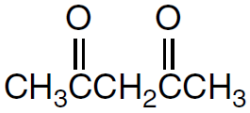
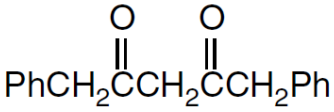
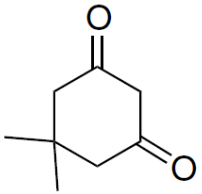
Solution	H_-[a]
1 *M* KOH	14.0
5 *M* KOH	15.5
10 *M* KOH	17.0
1.0 *M* NaOMe in MeOH	17.0
5.0 *M* NaOMe in MeOH	19.0
0.01 *M* NaOMe in 1:1 DMSO-MeOH	15.0
0.01 *M* NaOMe in 10:1 DMSO-MeOH	18.0
0.01 *M* NaOEt in 20:1 DMSO-EtOH	21.0

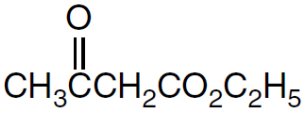
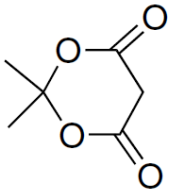
Alkylation with Enolates and Carbon Nucleophiles

Generation of Enolates by Deprotonation

- compounds with two stabilizing groups (malonates, β-ketoesters, β-diketones):

  - pK values slightly below ethanol and the other common alcohols
  - deprotonation – RONa, ROK
  - decarboxylation – extra step

Diketones	pK
	13.3
	13.35
	11.2

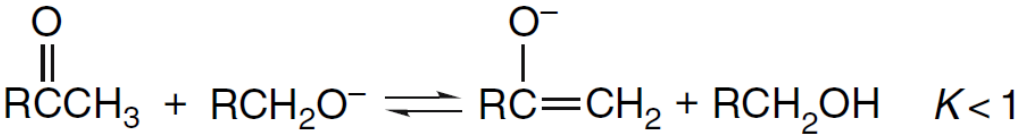
Ketoesters	pK
	14.2
Diesters	
$CH_2(CO_2C_2H_5)_2$	16.4
	7.3

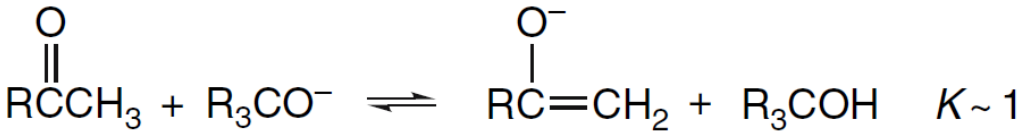
Alkylation with Enolates and Carbon Nucleophiles

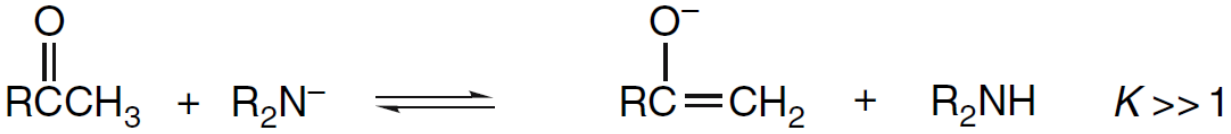
Generation of Enolates by Deprotonation

- monofunctional compounds (ketones, esters, amides):

  - pK > 20 values
  - deprotonation – aprotic solvents (THF, DME)
    – bases: amides (LDA, LTMP, pKa ~ 35)
    hexaalkyldisilylamines (LiHMDS, KHMDS, pKa ~ 30)
    „dimsyl“ anion (NaH/DMSO, pKa ~ 30)
    hydrides (NaH, KH) – preparation and purification
    other reagents (Ph_3CK, etc.)



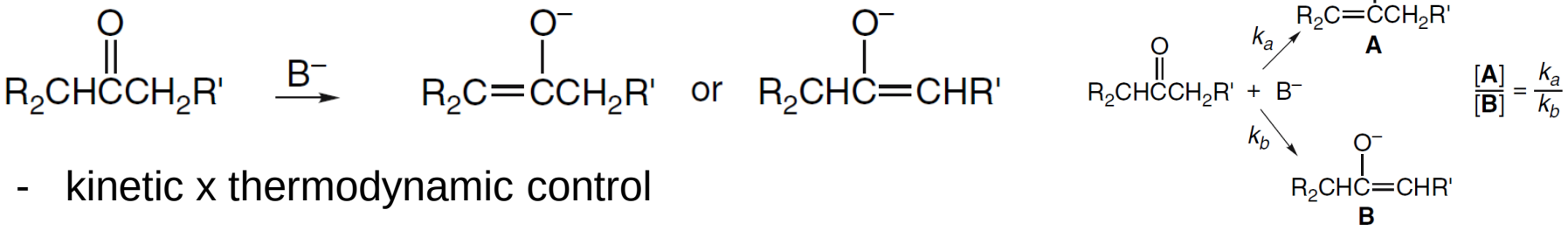




Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

- ketones and esters
- unsymmetrical dialkyl ketone can form two *regioisomeric* enolates:



- kinetic x thermodynamic control

kinetic control

- deprotonation is *rapid*, *quantitative*, and *irreversible*
- aprotic solvents (THF, DME)
- strong bases (LDA, LiHMDS) – Li better counter ion to kinetic enolates
- lower temperatures

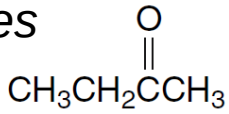
thermodynamic control

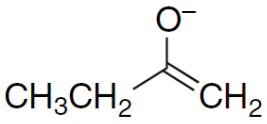
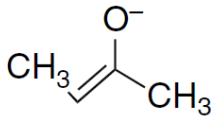
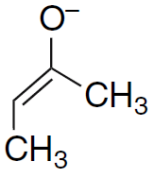
- protic solvents, HMPA (protonation – deprotonation)
- excess of ketone
- higher temperatures

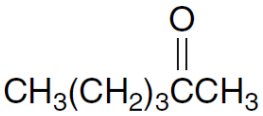
Alkylation with Enolates and Carbon Nucleophiles

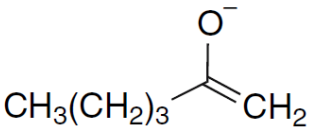
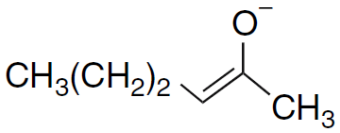
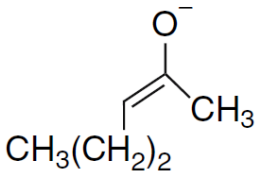
Regioselectivity and Stereoselectivity in Enolate Formation

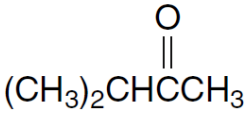
Examples

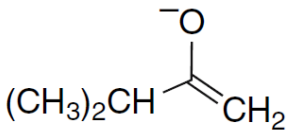
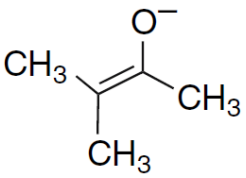


			
Kinetic, (LDA 0° C)	71%	13%	16%



			
Kinetic (LDA –78°C)	100%	0%	0%
Thermodynamic (KH, 20°C)	42%	46%	12%

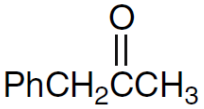


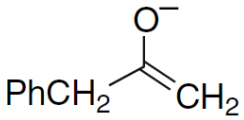
		
Kinetic (KHMDS, –78°C)	99%	1%
Thermodynamic (KH)	88%	12%

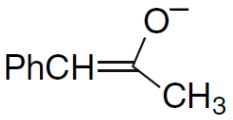
Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

Examples

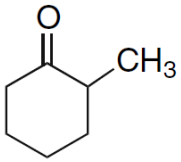


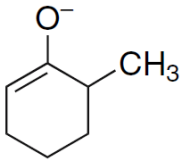


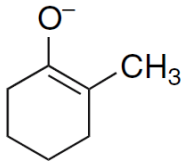


E,Z- combined

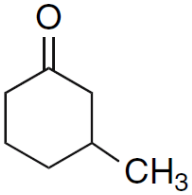
Kinetic (LDA 0°C)	14%	86%
Thermodynamic (NaH)	2%	98%

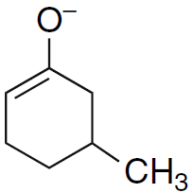


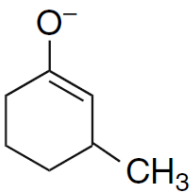




Kinetic (LDA, 0°C)	99%	1%
Thermodynamic (NaH)	26%	74%







Kinetic (Ph_3CLi)	82%	18%
Thermodynamic (Ph_3CK)	52%	48%

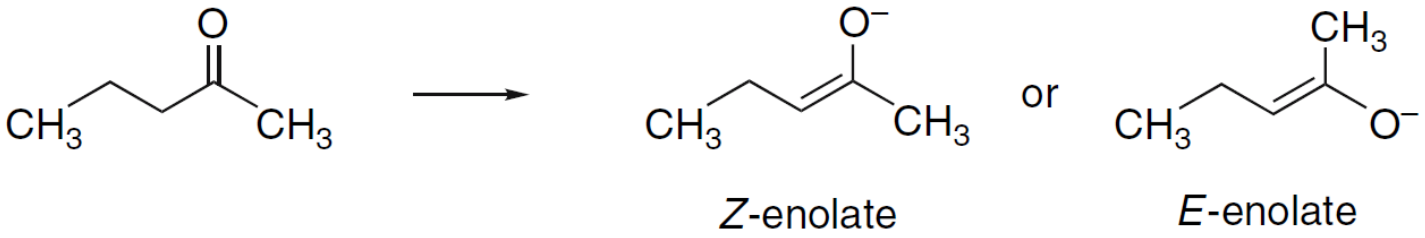
Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

E- and Z-enolates

- important for stereochemistry
- deprotonation of 2-pentanone:

  LDA in THF, with or without HMPA



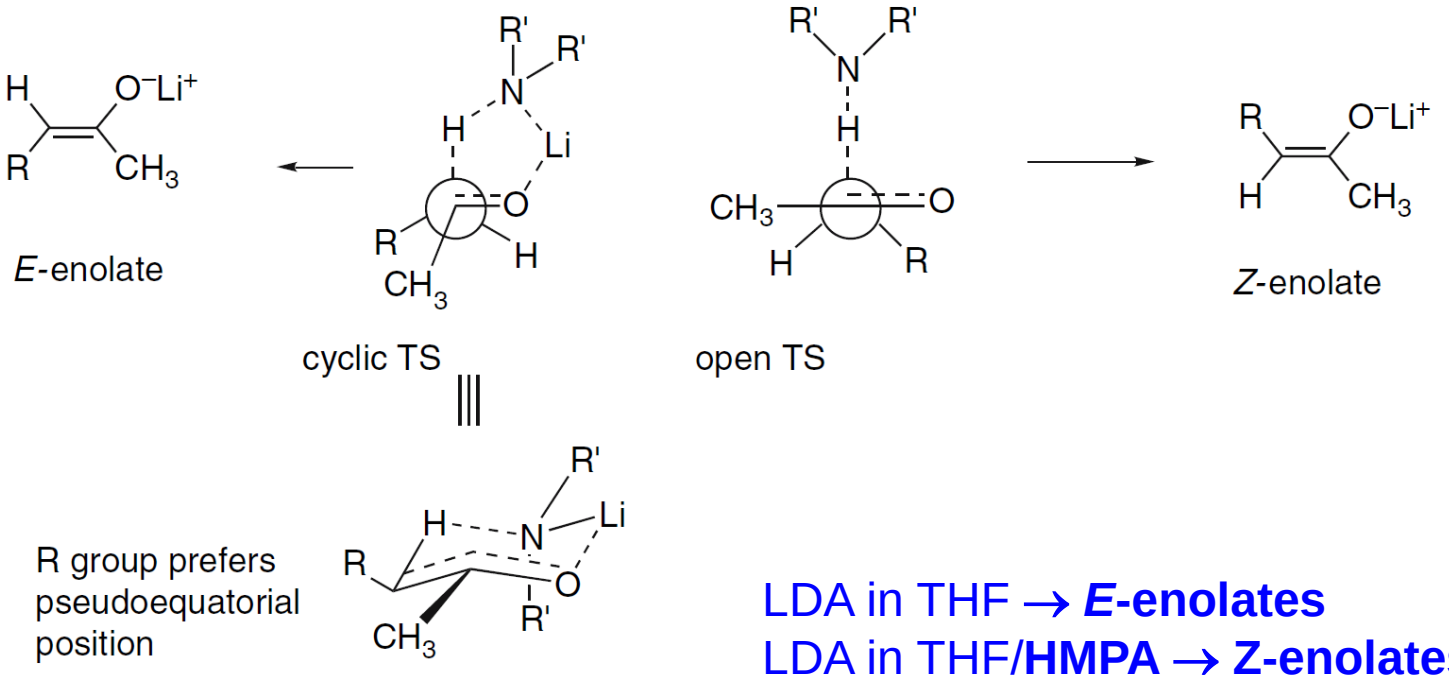
Ratio C(1):C(3) deprotonation		Ratio *Z*:*E* for C(3) deprotonation
0° C, THF alone	7.9	0.20
−60° C, THF alone	7.1	0.15
0° C, THF-HMPA	8.0	1.0
−60° C, THF-HMPA	5.6	3.1

Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

E- and Z-enolates

- cyclic x open TS
- presence of HMPA (0.75 M) – solvation of Li^+



LDA in THF → ***E*-enolates**

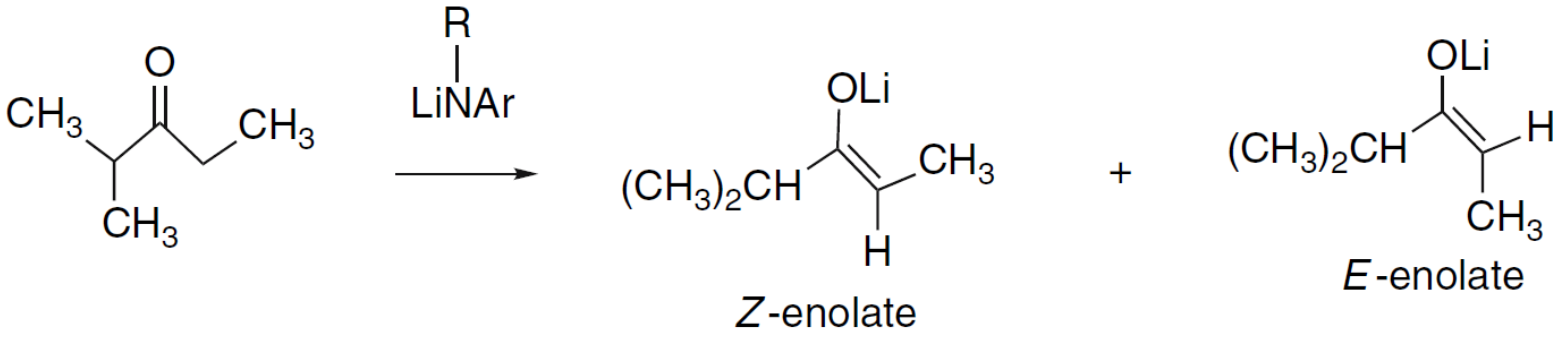
LDA in THF/**HMPA** → **Z-enolates**

Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

E- and Z-enolates

- LDA x **LiHMDS**, anilides
- *Z*-enolates prefered (looser TS, steric effects of the chair TS are reduced)



Z-enolate

E-enolate

$LiNH(C_6H_2Cl_3)$	98%	2%
$LiNPh_2$	100%	0%
$LiN(Ph)Si(CH_3)_3$	95%	5%

- *Z*-selectivity increased with reduced basicity of the amide anion

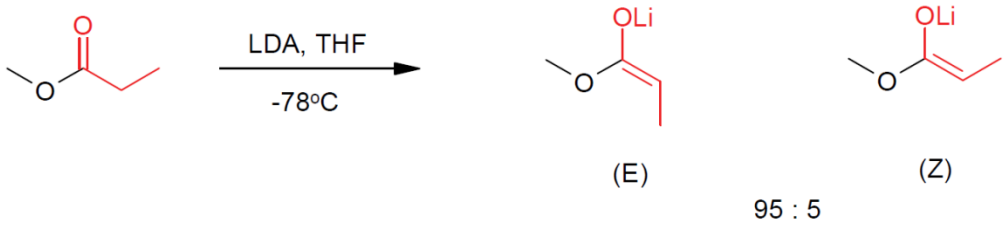
Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

E- and Z-enolates

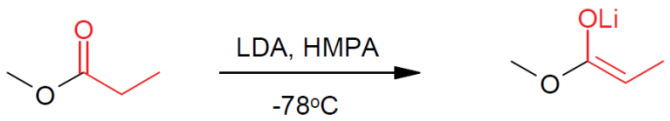
- LDA x LiHMDS + **additives**
- LiBr (LiX) – *E*-enolates

- *E*/*Z*-enolates of esters and amides

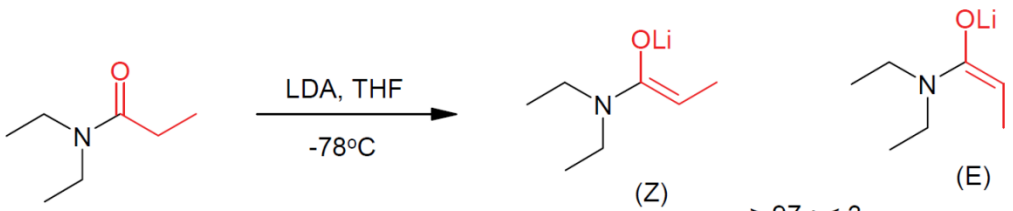


(E) (Z)

95 : 5



(Z)



(Z) (E)

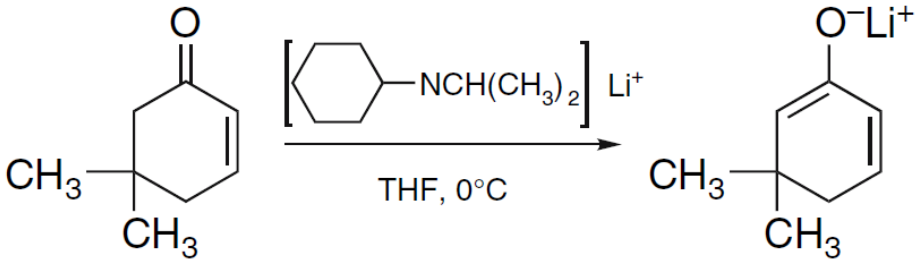
> 97 : < 3

Alkylation with Enolates and Carbon Nucleophiles

Regioselectivity and Stereoselectivity in Enolate Formation

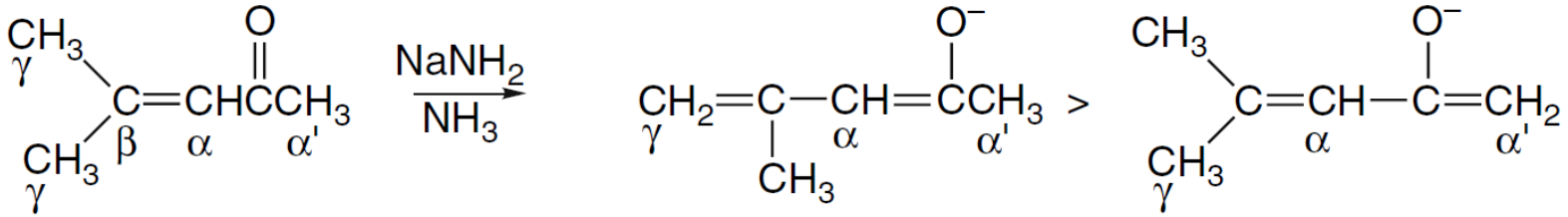
α,β-unsaturated ketones

- kinetic x thermodynamic control
- kinetic control (LDA/THF, etc.) → deprotonation of α´- H:



(only enolate)

- thermodynamic control (not Li^+ base, protic solvent, etc.)



1 major enolate (more stable)

2 (less stable)

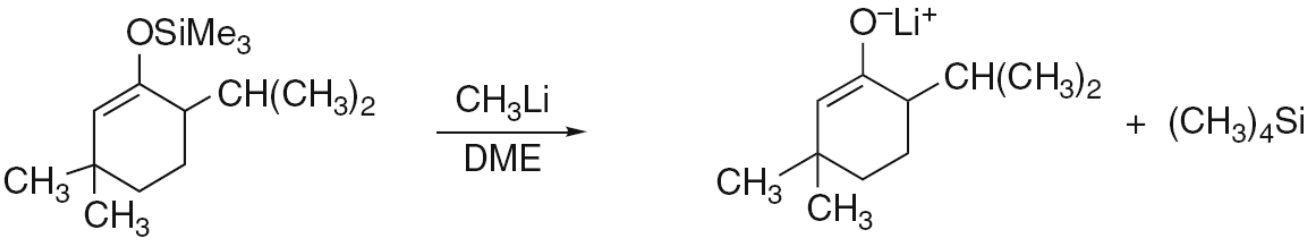
Alkylation with Enolates and Carbon Nucleophiles

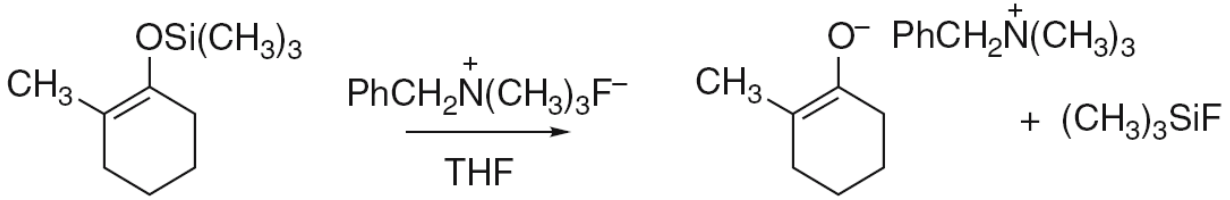
Other Means of Generating Enolates

Cleavage of TMS Ethers

- strong base (MeLi)
- fluoride anion reagents ($R_4N^+F^-$)
- alkoxides (KOtBu-thermodynamic control)

Examples



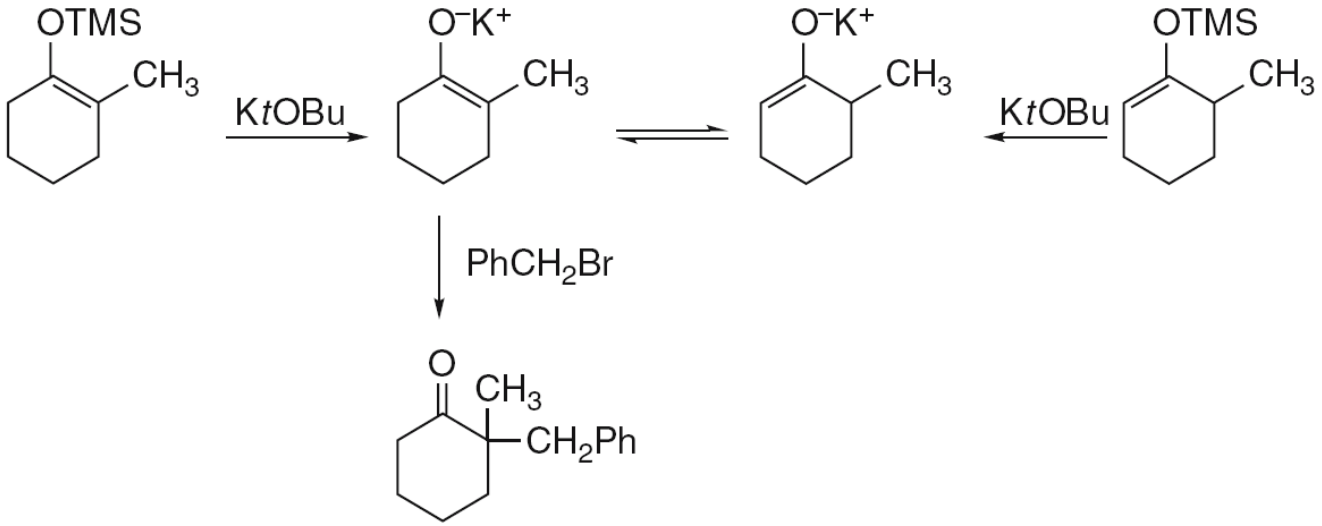


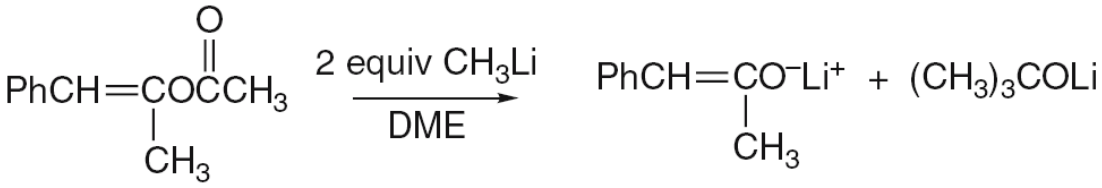
Alkylation with Enolates and Carbon Nucleophiles

Other Means of Generating Enolates

Cleavage of TMS Ethers

Examples



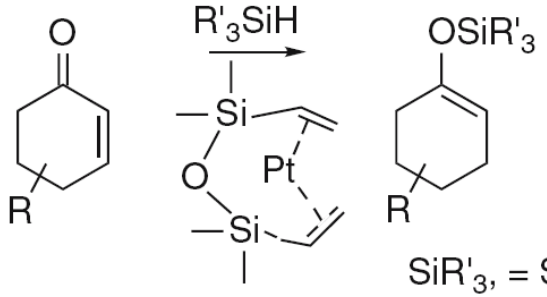


Alkylation with Enolates and Carbon Nucleophiles

Other Means of Generating Enolates

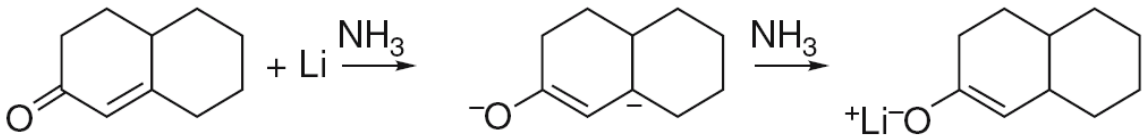
Reduction of α,β-Unsaturated Ketones

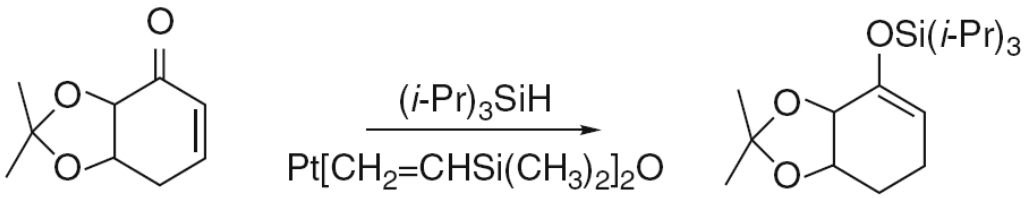
- Li/NH_3 or ROH (H source, excess)
- R_3SiH/Pt complex of divinyltetramethyldisiloxane



SiR'_3, = $Si(Et)_3$, $Si(i\text{-}Pr)_3$, $Si(Ph)_3$, $Si(Me)_2C(Me)_3$

Examples



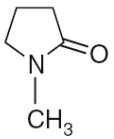


Alkylation with Enolates and Carbon Nucleophiles

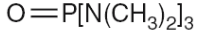
Solvent Effects on Enolate Structure and Reactivity

- rate of alkylation of enolates - strongly dependent on the solvent

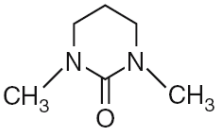
Solvent	Dielectric constant ϵ	Relative rate
Benzene	2.3	1
Tetrahydrofuran	7.3	14
Dimethoxyethane	6.8	80
N,*N*-Dimethylformamide	37	970
Dimethyl sulfoxide	47	1420



N-methylpyrrolidone (NMP)
ε = 32

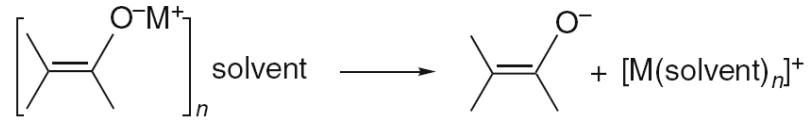


hexamethylphosphoric triamide (HMPA)
ε = 30



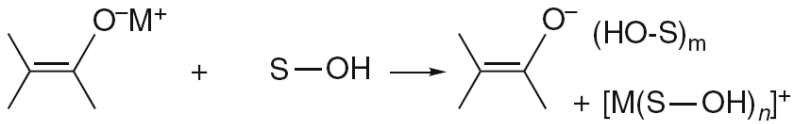
N,*N*′-dimethylpropyl-eneurea (DMPU)

- ↑ reactivity of enolates – unsolvated enolate
- dipolar aprotic solvents - excellent metal cation coordination ability (solvation, dissociation from ion pairs)
  - good cation solvators, poor anion solvators
- polar protic solvents - coordination to cation and anion



aggregated ions

dissociated ions



solvated ions

Alkylation with Enolates and Carbon Nucleophiles

Solvent Effects on Enolate Structure and Reactivity

Ether solvents (THF, DME)

- the most common in enolate alkylation
- reduced reactivity of aggregeted enolates
- suitable for enolate generation (kinetic control)
- suitable for enolate genetation (thermodynymic control) – additives:
    - HMPA, DMPU
    - TMEDA
    - crown ethers

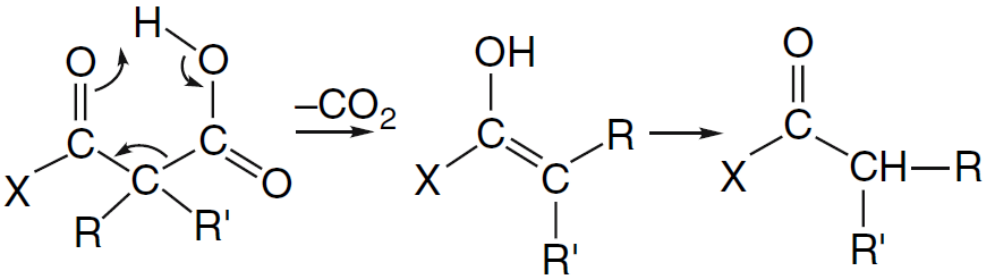
- Appendix

- reactivity of enolates affected by the metal counterion
- order of reactivity: $Mg^{2+} < Li^{+} < Na^{+} < K^{+}$

Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Highly Stabilized Enolates

- first class of carbanion alkylation compounds (acidic H)
- compounds with two stabilizing groups (malonates, β-ketoesters, β-diketones):
  - deprotonation – R´ONa, R´OK, K_2CO_3, NaH
  - alkylation (S_N2): 1°R-LG – highly reactive (LG = X, $SO_3R´´$)
    2°R-LG – slow, moderate yields
    3°R-LG – elimination
  - dialkylation: sufficient base
    sequential (two different R-LG)
    cyclization (LG-R-LG) – relative rates:
    650 000 : 1 : 6500 : 5…… three-, four-, five-, six-membered rings
  - decarboxylation x hydrolysis-decarboxylation:

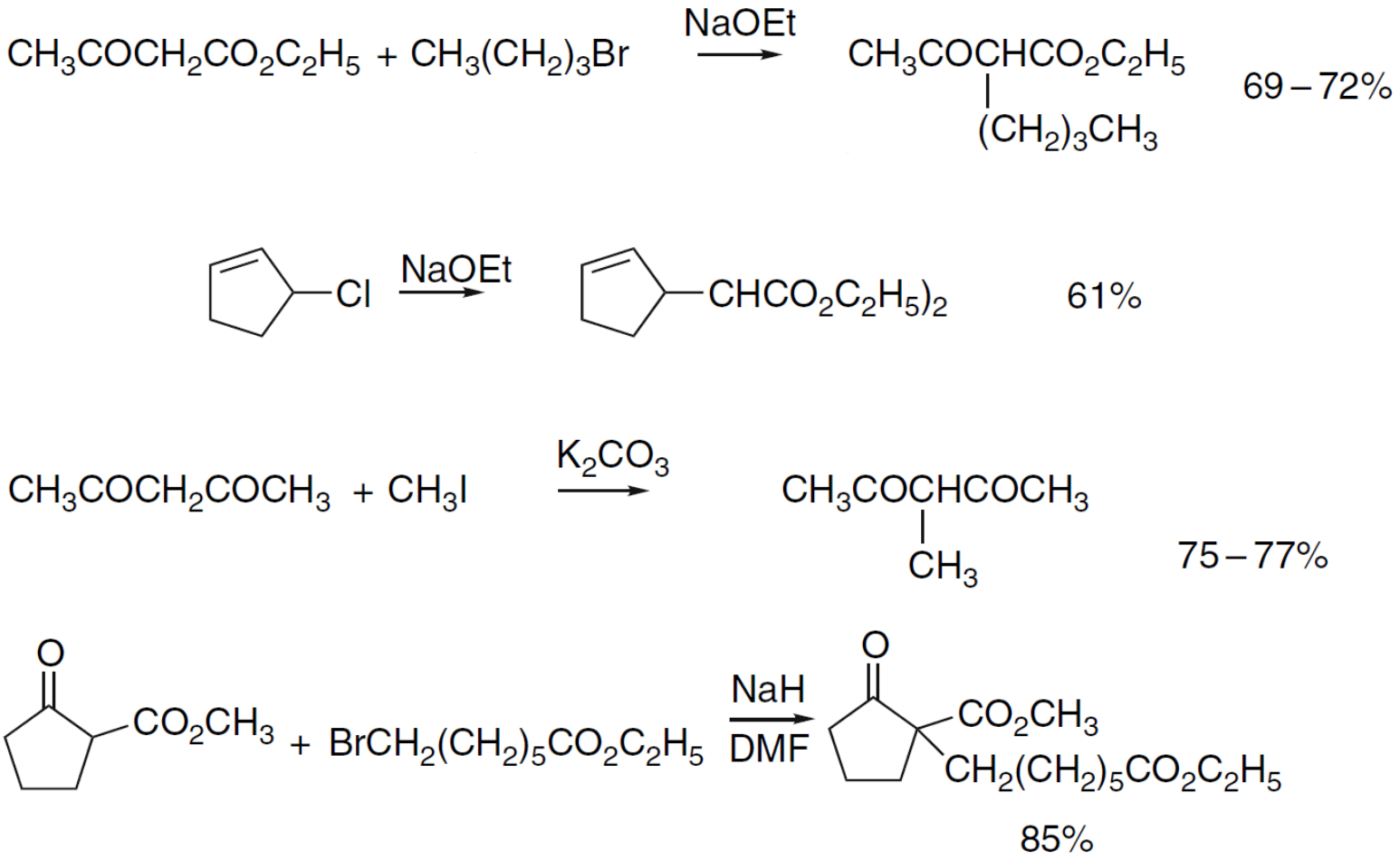


β-keto acid: X = alkyl or aryl = ketone
substituted malonic acid: X = OH = substituted acetic acid

Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Highly Stabilized Enolates

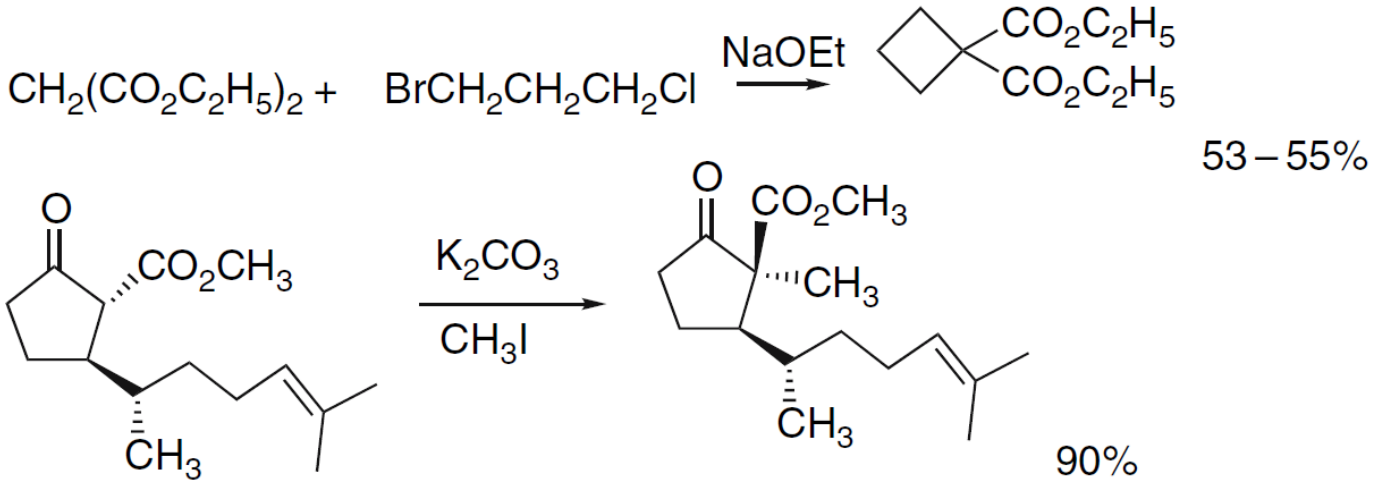
Examples



Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Highly Stabilized Enolates

Examples



$$CH_2(CO_2C_2H_5)_2 + C_7H_{15}Br \xrightarrow{NaOBu} C_7H_{15}CH(CO_2C_2H_5)_2$$

$$C_7H_{15}CH(CO_2C_2H_5)_2 \xrightarrow{H_2O,\ ^-OH} \xrightarrow{H^+} C_7H_{15}CH(CO_2H)_2$$

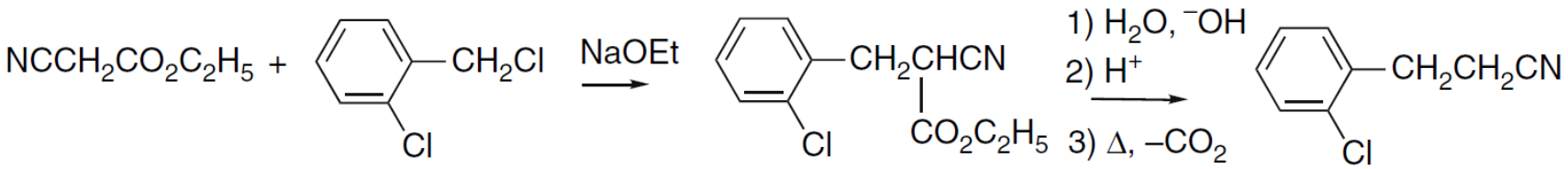
$$C_7H_{15}CH(CO_2H)_2 \xrightarrow{\Delta} C_8H_{17}CO_2H + CO_2$$

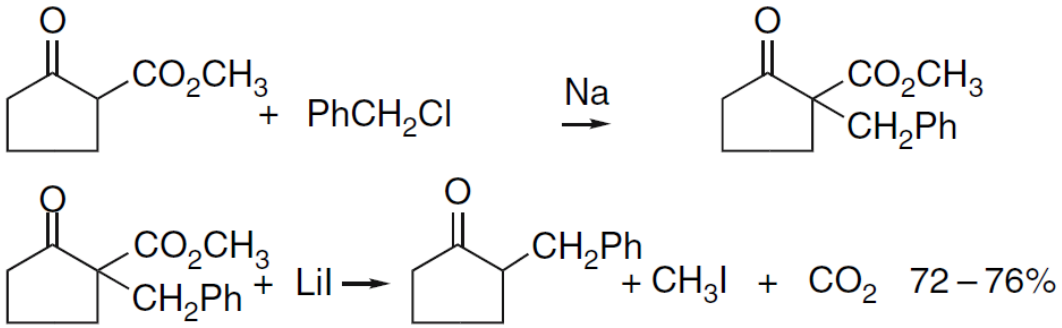
66 – 75%

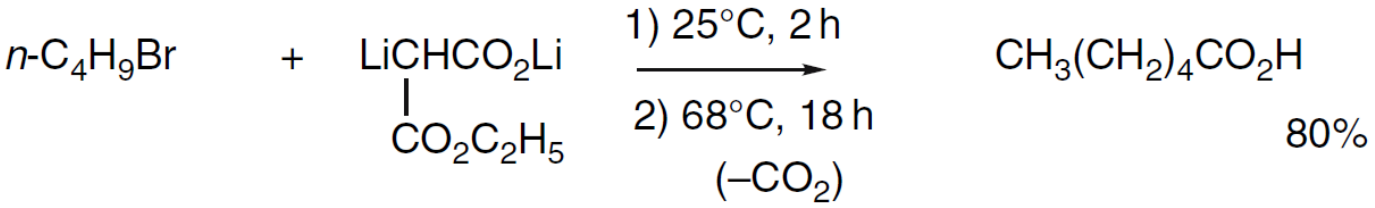
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Highly Stabilized Enolates

Examples



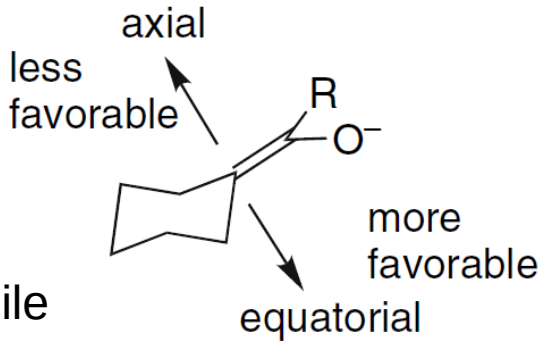




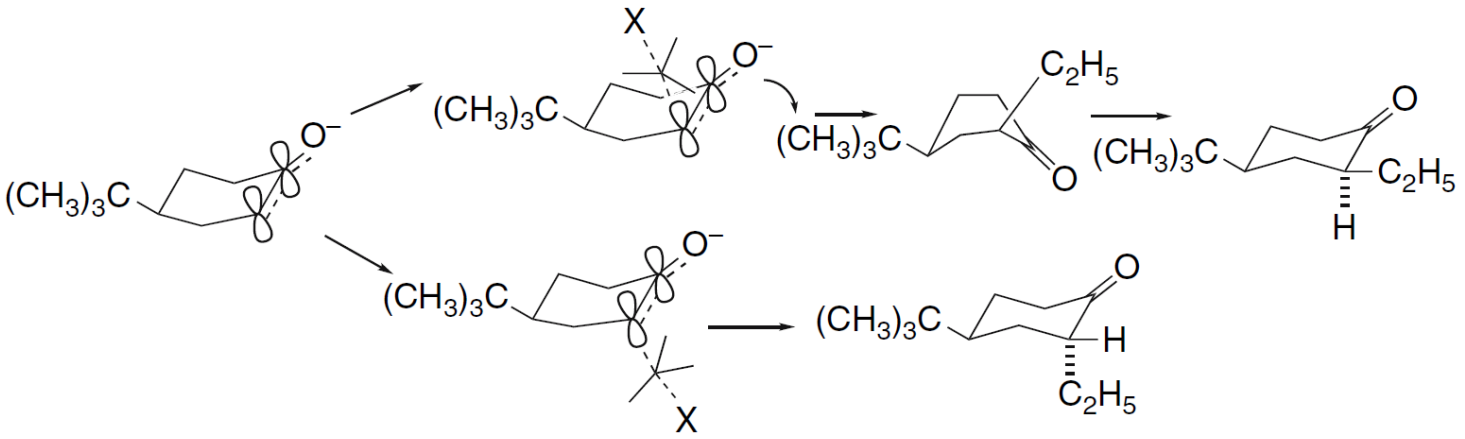
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Ketone Enolates

- to avoid hydrolysis-decarboxylation step
- deprotonation – LDA, etc. (see ↑)
- alkylation (see ↑) – stereoelectronically prefered perpendicular attack
  - differentiation – sterical hindrance x chelation effect
    – conformation of enolate
    – stereoelectronical effects



- cyclic ketones:
  1) cyclohexanone:
     - slight preference of equatorial attack of electrophile
     - C(4)-substituents (low differentiation)



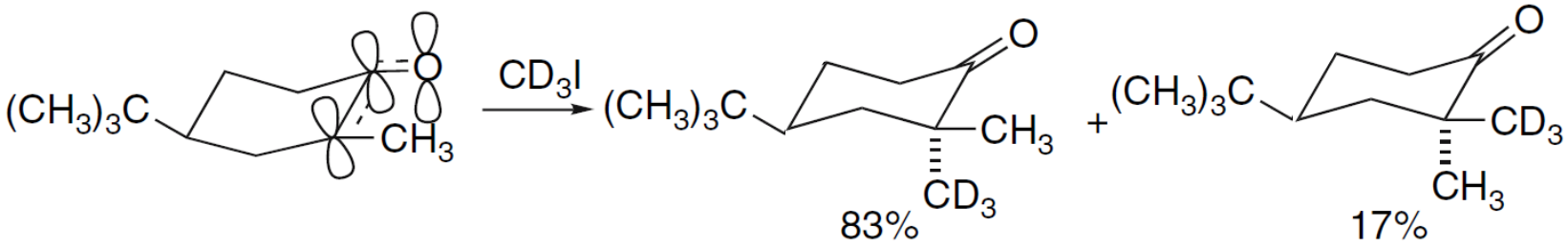
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Ketone Enolates

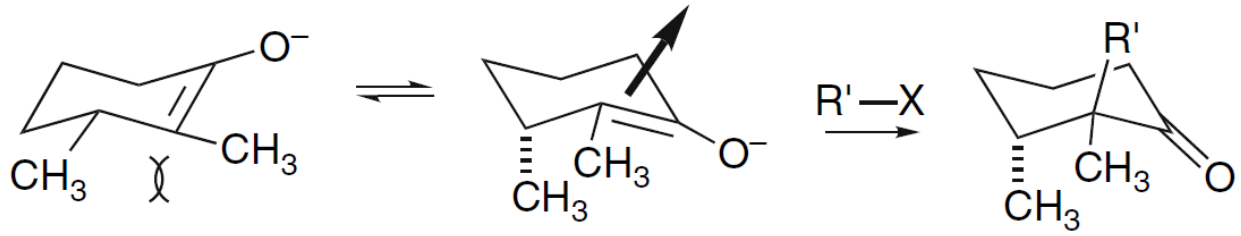
- cyclic ketones:

1) cyclohexanone:

- C(4) and C(2)-substituents (high differentiation) – axial attack



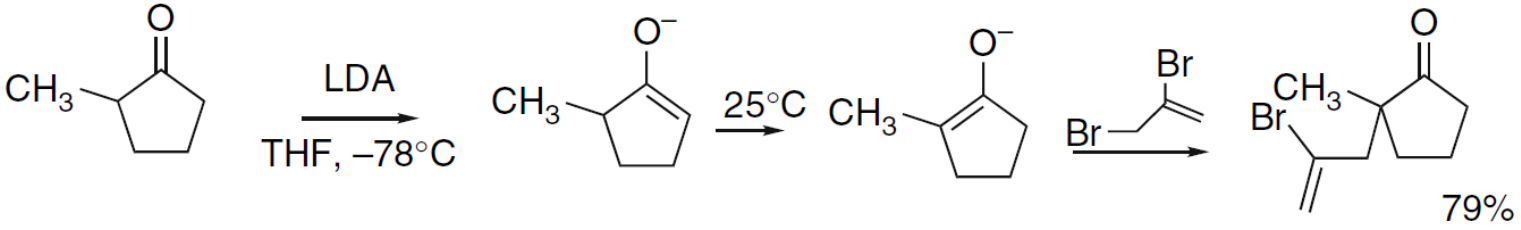
- C(3) and C(2)-substituents (high differentiation) – *trans* attack

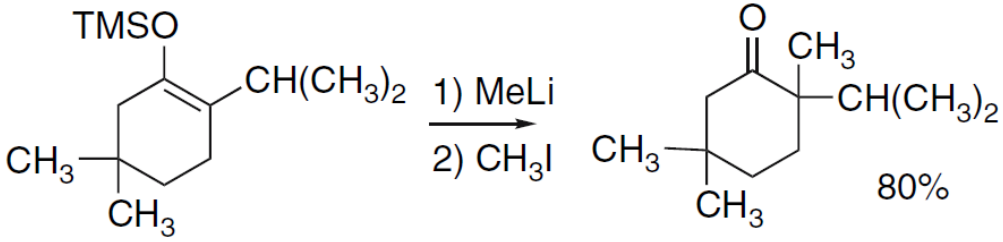


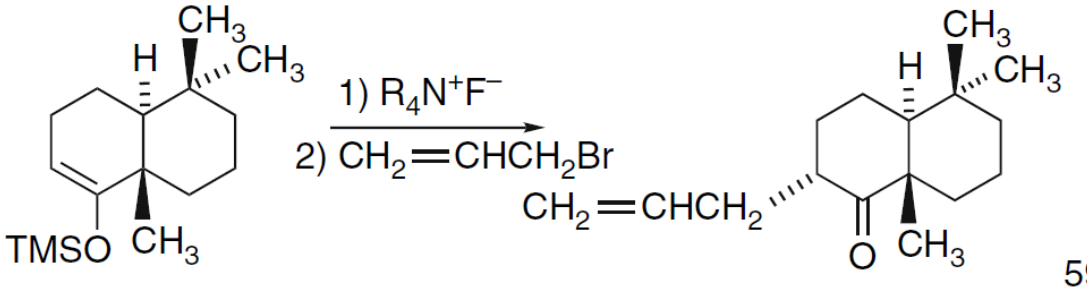
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Ketone Enolates

Examples



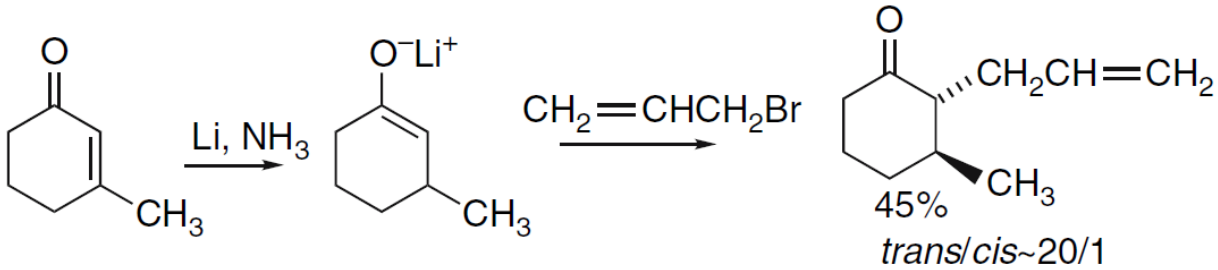


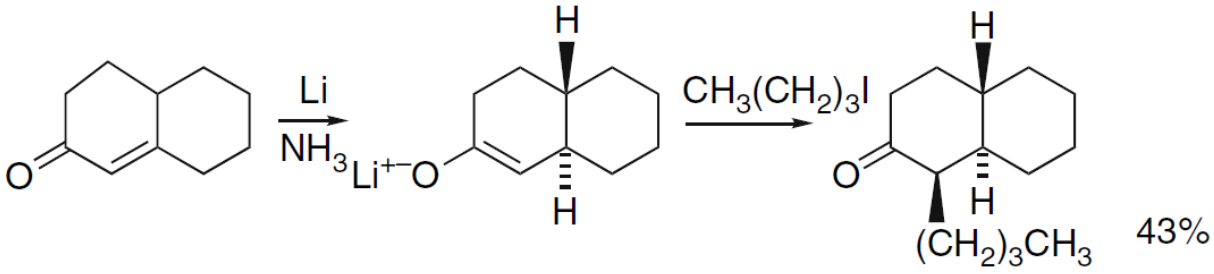


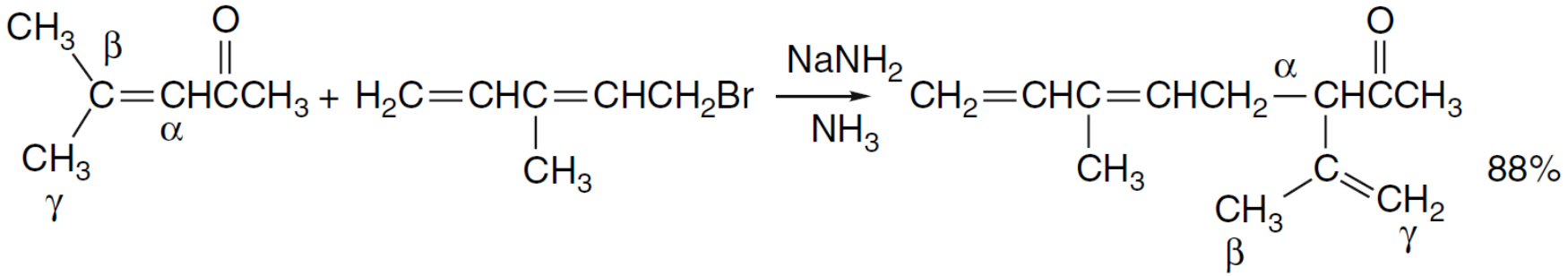
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of Enolates – Ketone Enolates

Examples







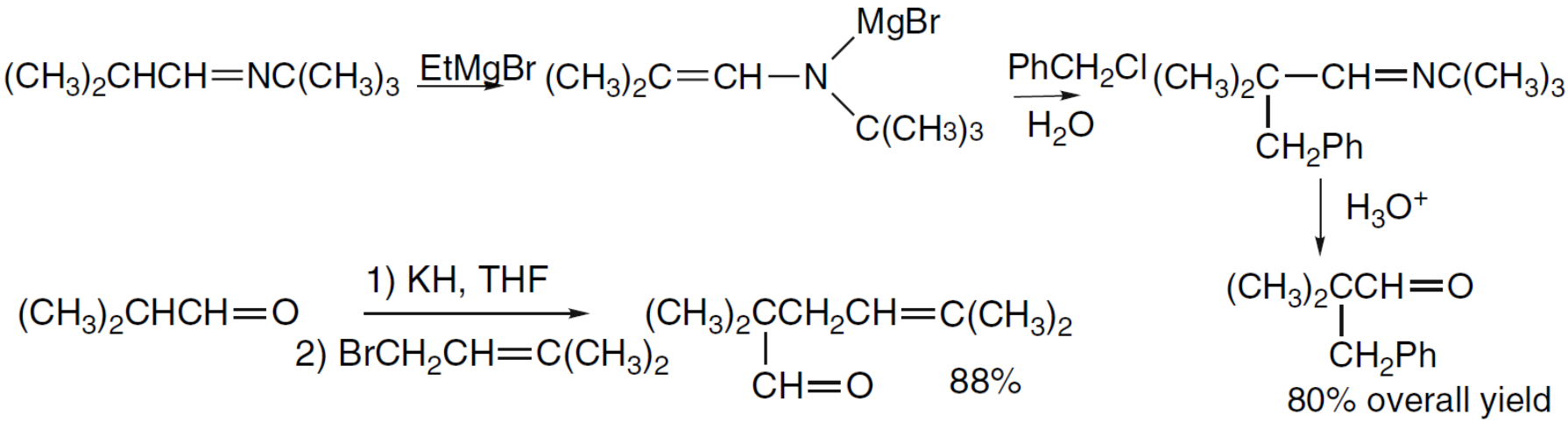
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of RCHO, RCOOH, RCOOR´, RCONR´R´´, RCN

Aldehydes

- not very common, aldol reactions prefered
- base system ($NaNH_2/NH_3$, KH/THF) – rapid, quantitative
- *via* enamine intermediates – more nucleophilic

Examples

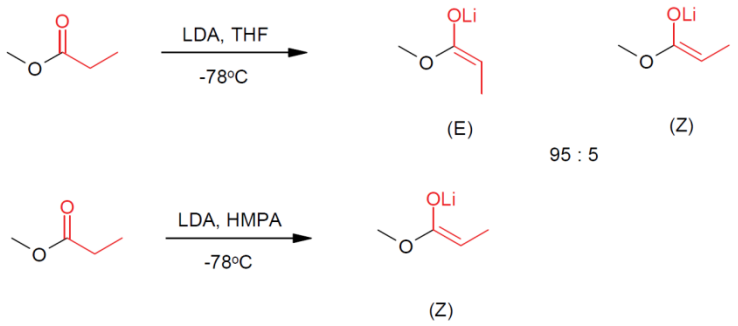


Alkylation with Enolates and Carbon Nucleophiles

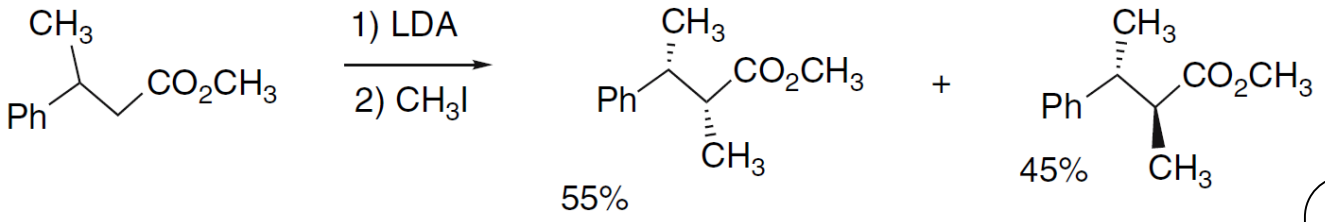
Alkylation of RCHO, RCOOH, RCOOR´, RCONR´R´´, RCN

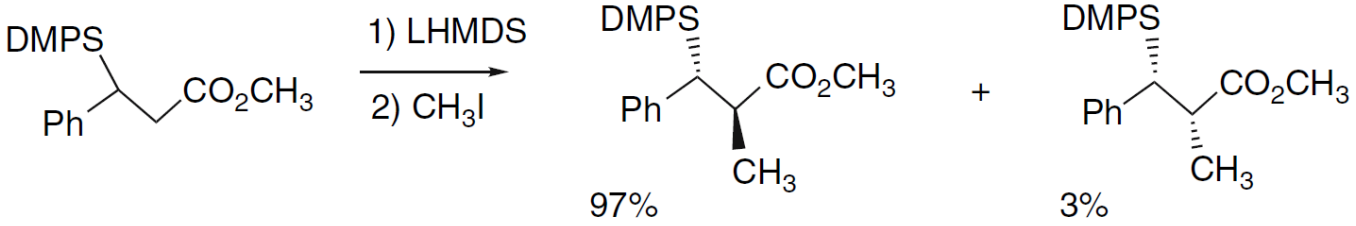
Esters

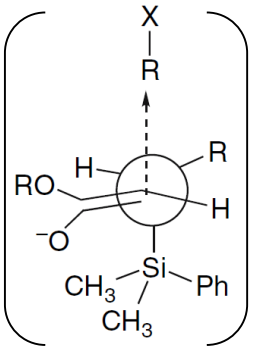
- esters enolates less stable then ketone enolates (elimination of RO^-)
- Li-enolates (low temperatures)
- strong base – LDA, LiHMDS
  (weak RONa – condensation)
- solvent – THF, HMPA
- alkylation – RI, RBr
- stereochemistry – steric factors



Examples







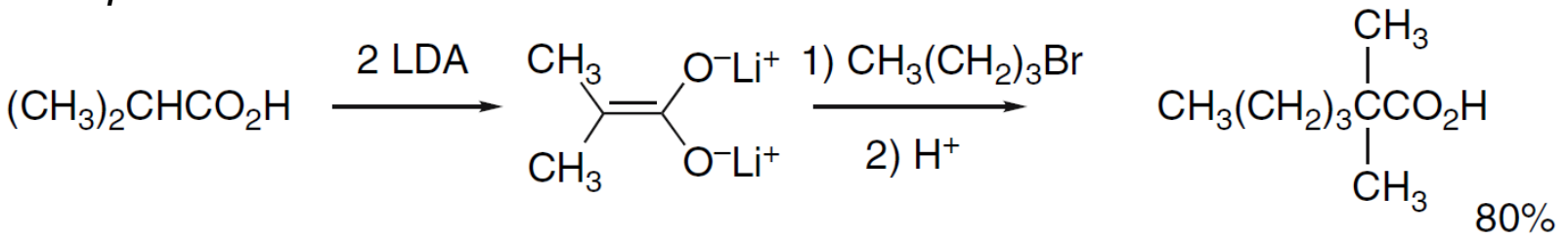
Alkylation with Enolates and Carbon Nucleophiles

Alkylation of RCHO, RCOOH, RCOOR´, RCONR´R´´, RCN

Carboxylic acids

- 2 eq. of base (LDA)
- nuclephilic x basic

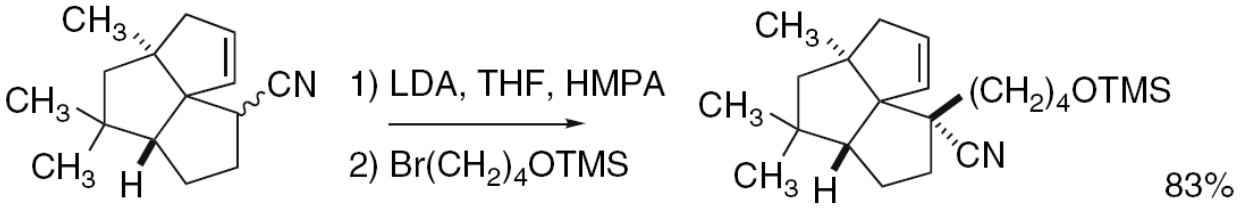
Example



Nitriles

- CH_3CN $(pK_{DMSO} = 31.3)$

Example

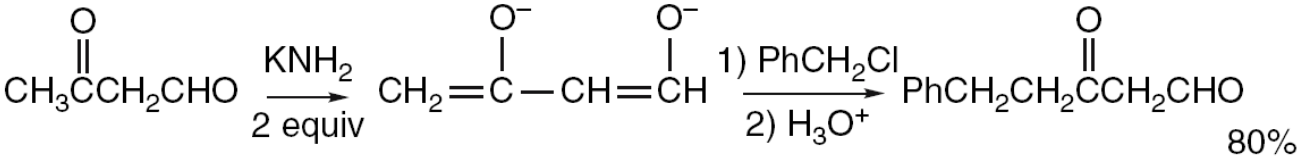


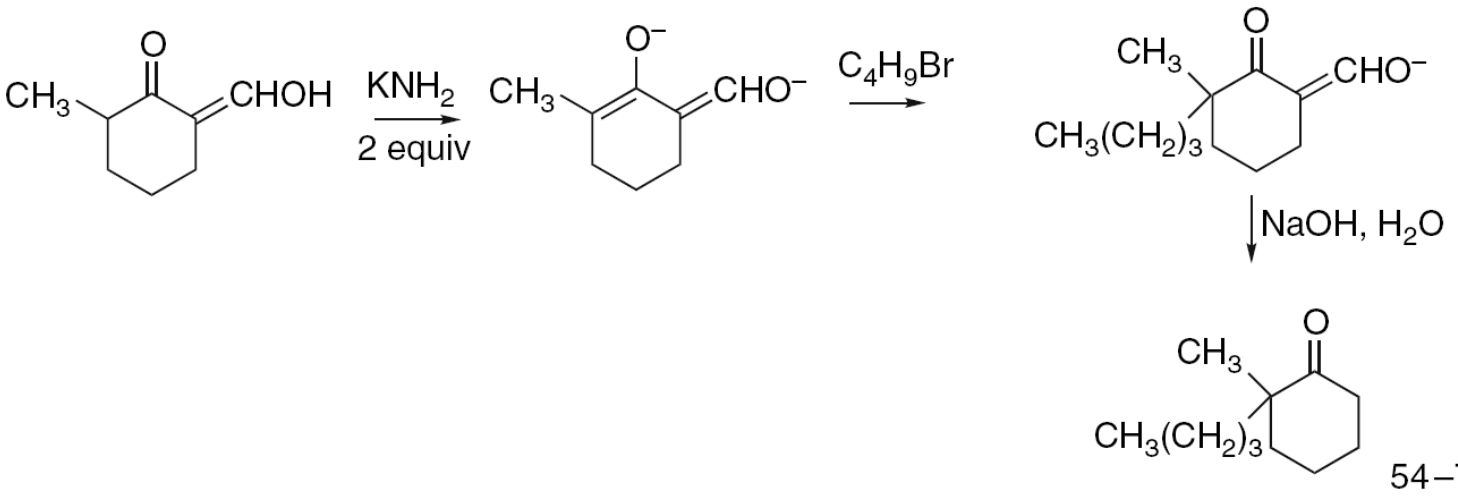
Alkylation with Enolates and Carbon Nucleophiles

Generation and Alkylation of Dianions

- 1,3-dicarbonyl compounds
- 2 sequential deprotonation
- very strong base (LDA, $NaNH_2$)
- alkylation of dianions - at the more basic carbon

Examples

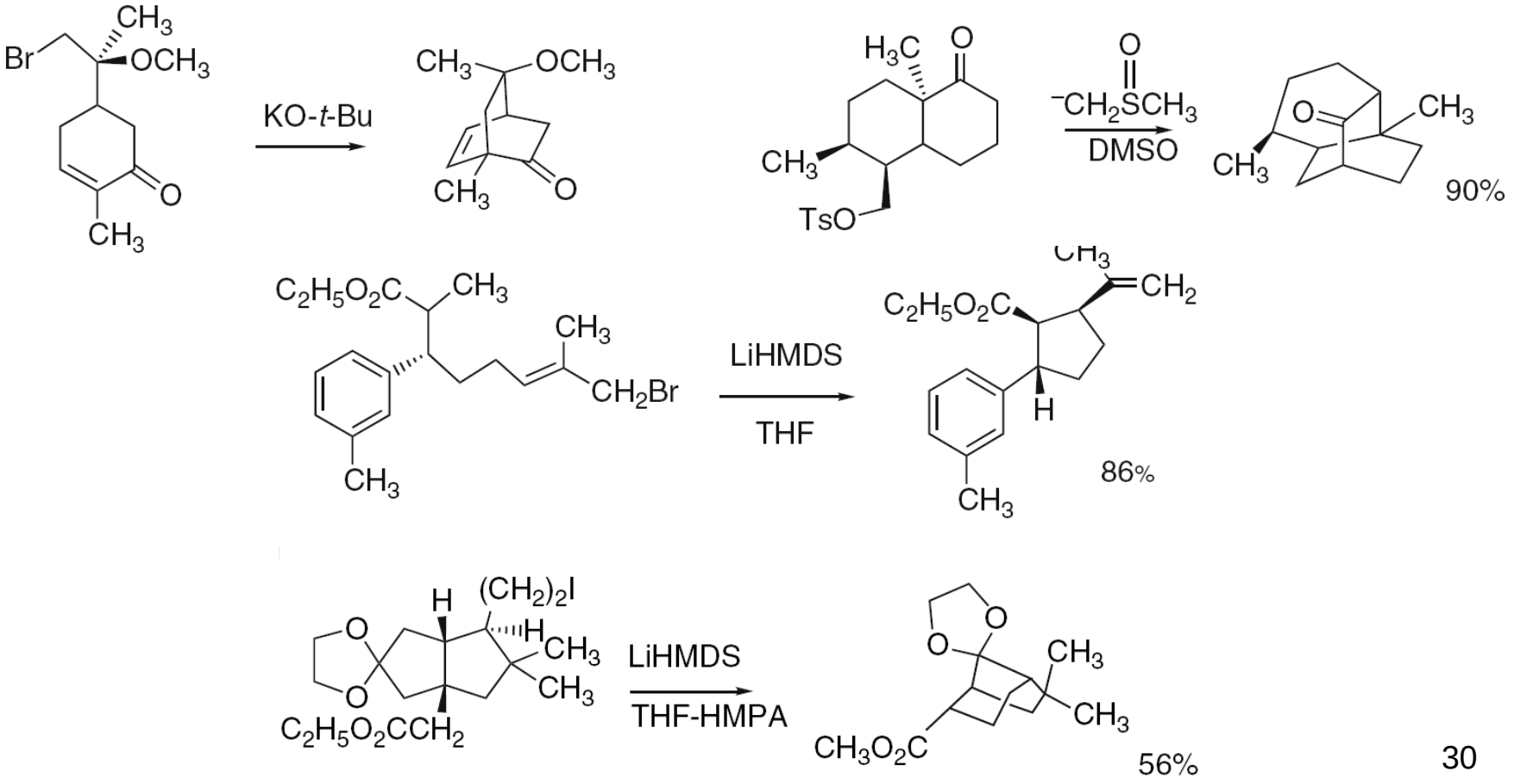




Alkylation with Enolates and Carbon Nucleophiles

Intramolecular Enolate Alkylation

Examples



Nitrogen analogs of Enols and Enolates:
Enamines and Imine anions

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